REMARKS

STATUS OF THE CASE

In the Office Action issued April 29, 2008 all of the claims were rejected under 35 U.S.C. §112 1st Paragraph and Claims 236-241, 243-257 and 260-274 were rejected under 35 U.S.C. §103(a). Claims 242 and 259 are presently withdrawn. In this response, Applicant traverses all rejections.

SPECIFICATION AMENDMENT

The specification stands objected to for certain informalities. The disclosure is objected to because it contains embedded hyperlinks and/or other form of browser-executable code. Furthermore, the specification stands objected to under 37 CFR 1.821(d) for failing to refer to a sequence by use of a Sequence Identifier. Specifically, Figure 6 contains four illustrations containing 10 or more nucleotide sequences without a Sequence Identifier. Applicant has amended the specification according to the Examiner's suggestions by adding the sequence identifiers SEQ ID NO: 16-19 in the brief drawing description for Figure 6. Furthermore, Applicant is submitting herewith a substitute copy of the Sequence Listing and an electronic copy of the **substitute** computer readable form of the substitute Sequence Listing in compliance with the requirements of 37 CFR 1.821, 1.822 and 1.823.

Please enter the enclosed substitute copy of the Sequence Listing into the PCT application number PCT/US2004/021451 following paragraph [0086] of the application. No new subject matter has been added.

I hereby state that the substitute Sequence Listing information recorded in computer readable form is identical to the substitute copy of the written (paper version) Sequence Listing being submitted herewith in accordance with 37 C.F.R. 1.821(f) and includes no new matter as required by 37 CFR 1.821(e), 1.821(f), 1.821(g), 1.825(b) and 1.825(d). Therefore, reconsideration and withdrawal of this objection is respectfully requested.

The specification is objected to because paragraphs [0065] (partial)-[0075] (partial) are missing. Applicant has downloaded the filed Application dated December 22, 2005 from public PAIR and can verify that paragraphs [0065]-[0075] are on pages 38-40 are present and are complete. Applicant respectfully requests the Examiner to reconsider and withdraw the present objection.

APPLICANT'S CLAIMS COMPLY WITH 35 U.S.C. §112 1ST PARAGRAPH

In the April 29, 2008 Office Action, Claims 236-241, 243-258 and 260-274 stand rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to reasonably provide enablement for a method for producing a heterologous polypeptide in any cell or any IRES from any source or any stimulus for synthesis of an RNA complementary to an RNA transcript of the recombinant RNA. Further, the Office Action asserts that the specification does not enable a person of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. (Office Action at page 4). This rejection is respectfully traversed.

At the outset, Applicant thanks the Examiner for finding that the specification is enabling for a method of producing a heterologous polypeptide in a plant comprising a) providing a transgenic plant comprising a DNA molecule containing a promoter operably linked to a DNA sequence containing a sequence complementary to a coding sequence for a heterologous polypeptide, a sequence complementary to an IRES from a plant virus and a 3' UTR of a first positive strand single-stranded RNA virus; b) growing the transgenic plant; and c) stimulating synthesis of an RNA complementary to an RNA transcript of the recombinant DNA by infecting the transgenic plant with a second positive strand single-stranded RNA virus closely related to the first one. (Action at page 3, and page 4). Nevertheless, Applicant submits that all of the claims are fully enabled.

In essence, the Examiner appears to allege two main points.

- The specification generally, teaches how to synthesize a complementary copy of a recombinant RNA comprising the transgene encoding a complementary sequence of a heterologous polypeptide; but
- The specification does not teach specifics regarding how to translate the recombinant RNA comprising the transgene encoding a complementary sequence of a heterologous polypeptide using an IRES from any source in any cell.

As discussed below, Applicant respectfully submits that the specification enables one of ordinary skill in the art how to make and use the claimed invention.

THE BREADTH OF THE CLAIMS ARE FULLY ENABLED AS TO ALL IRES COMBINATIONS FOR ALL TRANSGENIC CELLS

Claim 236 is directed to a method of producing a heterologous polypeptide, the method comprising:

a) providing a transgenic plant or transgenic cell comprising a recombinant DNA molecule comprising a promoter operably linked to a DNA sequence comprising, in the 5' to 3' direction,

i) a sequence complementary to a coding sequence for a heterologous polypeptide;

ii) a sequence complementary to an internal ribosome entry site;

iii) a 3' UTR of a first positive strand single-stranded RNA virus;

b) growing the transgenic plant or transgenic cell; and

c) providing a stimulus to the transgenic plant or transgenic cell for synthesis of an RNA complementary to an RNA transcript of the recombinant DNA.

The method of Claim 236 provides for effective translation of a transgene encoded by the recombinant RNA, only when a transgenic plant or plant cell has been stimulated with an external stimulus such as a second single-strand RNA virus. Once the transgene has been transcribed to a (+) sense or mRNA form using an RNA-dependent RNA polymerase, the mRNA comprising an IRES and a sense copy of the heterologous polypeptide downstream of said IRES enables the host cell translation machinery can translate said polypeptide using the expressed IRES.

The Action alleges that the specification fails to reduce to practice the present invention. (Action at page 5). In support of this allegation, the Action cites Gleba et. al. (U.S. Patent Application Publication Number 2004/0055037 published March 18, 2004). Gleba et al. state that: "Existing IRES elements isolated from animal viruses do not support translation in animal cells." (Gleba et al., at par. [0013] and Action at page 6). Applicant respectfully disagrees with this assertion in Gleba. First, no reference is provided in Gleba or in the present Office Action to support the conclusion that IRES elements isolated from animal viruses do not support translation in plant cells. Second, Applicant provides a reference that fully supports the use of animal cell viruses (encephalomyocarditis, EMCV) in plant systems to translate a viral (+) sense

or mRNA strand encoding a heterologous polypeptide. Urwin, P. et al. (2000), "Functional characterization of the EMCV IRES in plants" The Plant Journal 24:583-589. (Applicant has attached an abstract of Urwin, P. et al. as a courtesy copy for the Examiner herein).

Thus, animal viral IRES elements have been shown to work in plant cells. One of ordinary skill in the art can, therefore, without undue experimentation construct a DNA molecule comprising a compatible complementary IRES sequence derived from either plant, animal or viral sources for expression and use in transgenic plants and transgenic cells in accordance with the various embodiments of the present invention.

With respect to the Action's assertion that undue experimentation would have been required for a person skilled in the art to practice the invention using any IRES element from any source, the Applicant respectfully disagrees. The experimentation required to match the appropriate host cell with a suitable IRES would not be undue considering the teachings in Applicant's specification, in particular, as shown in Examples 1-5 and the knowledge readily obtainable or possessed by one of ordinary skill in the art at the time of filing. At the time of filing the present application, one of ordinary skill in the art possessed a high level of skill, *i.e.* a Ph.D. molecular biologist or plant biologist. The person of ordinary skill in the art would have had within their possession routine assays to determine whether a particular IRES sequence(s) could be inserted into the recombinant DNA construct of the present embodiments. One such example includes the dicistronic translation assay which has been used in plant, yeast and HeLa cells to test the efficiencies of different IRES elements from three different kingdoms, plants, yeast and animal cells. (See Dorokhov, Y.L., et al., (2002), "Polypurine (A)-rich sequences promotes cross-kingdom conservation of internal ribosome entry" Proc. Natl. Acad. Sci., 99(8):5301-5306. A copy of Dorokhov, Y.L., et. al. is provided as a courtesy copy herein).

Once the recombinant DNA is transcribed into the complement copy of the recombinant RNA strand comprising the complementary IRES sequence and complementary polypeptide sequence, the recombinant RNA strand can be isolated and tested in a transcription/translation assay to determine whether the uncapped recombinant RNA strand containing the IRES can be translated in plant or animal cells. Such assays include the cell free rabbit reticulocyte *E.coli* and the wheat germ translation kits and coupled translation/transcription kits commercially available from several vendors including Ambion (Applied Biosystems), Promega, Qiagen and Boehringer Mannheim. Although some experimentation may be required to practice the full

scope of the claimed subject matter, Applicant respectfully asserts that such experimentation is merely routine to those of ordinary skill in the art and not undue. MPEP § 2164.06.

Accordingly, Applicant respectfully requests that the present rejection of Claims 236-241, 243-258 and 260-274 under 35 U.S.C. §112, first paragraph be reconsidered and withdrawn.

CLAIMS ARE NOT OBVIOUS OVER THE COMBINED REFERENCES CITED OF RECORD

Claims 236-241, 243-257 and 260-274 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Teycheney et al. (2000, Journal of General Virology 81:1121-1126, herein referred to as "Teycheney") in view of Basso et al. (1994, Journal of General Virology 75:3157-3165, herein referred to as "Basso"). This rejection is respectfully traversed.

Teycheney is drawn to homozygous R2 transgenic tobacco plants expressing Cucumber mosaic virus (CMV) or Lettuce mosaic virus (LMV) constructs (coat proteins with or without their respective 3'UTR) and were infected with related cucumovirus TAV-P virus in the case of CMV constructs and CMV-R, potyvirus TEV, Tobacco vein mottling virus (TVMV), Turnip mosaic virus (TuMV), Potato virus Y (PVY), Pepper mottle virus (PepMoV) and Plum pox virus (PPV) in the case of LMV constructs. Generally, Teycheney states that the some of the potyviruses TVMV, TEV and PepMoV were able to infect transgenic cells and synthesize a complementary copy of the (-) strand transcripts of the originally infected viral genome while others were not able to synthesize a complementary copy of the (-) strand transcripts (PVY, TuMV and PPV). Teycheney further states that the presence of the last 269 nucleotides of the CMV-R 3'UTR or the last 185 nucleotides of the LMV-O 3'UTR is necessary to promote the synthesis of a complementary RNA from transcripts of a transgene. (Teycheney at page 1124, col. 2, 1st and 2nd paragraphs).

Basso is drawn to the experimental confirmation that turnip mosaic potyvirus (TuMV) most likely has a ^{7}m-cap independent translation mechanism and is likely that ribosomes in the host bind to an internal site on the TuMV 5'NTR. This internal site was suggested to be an IRES. (Basso at page 3162).

It is respectfully submitted that neither reference discloses the use of a DNA or RNA nucleic acid encoding a complementary sequence encoding a 3'-UTR, a complementary IRES element and a complementary sequence of a heterologous polypeptide constructed for expression of a heterologous polypeptide after a subsequent activation or stimulation.

In contrast, Claim 236 and 260 are drawn to a DNA molecule comprising in the 5'-3' direction,

i) a sequence complementary to a coding sequence for a heterologous polypeptide;

ii) a sequence complementary to an internal ribosome entry site; and

iii) a 3' UTR of a first positive strand single-stranded RNA virus....

Furthermore, Claim 236 recites additional method steps including: growing the transgenic plant or transgenic cell; and providing a stimulus to the transgenic plant or transgenic cell for synthesis of an RNA complementary to an RNA transcript of the recombinant DNA.

Applicant respectfully asserts that there is no teaching, disclosure or suggestion to translate the recombinant RNA produced in Teycheney using an IRES. One of the present invention's objectives is to provide a system for transgene expression in which the level of expression of the transgene in an unstimulated cell is not measurably greater than in a non-transgenic cell of the same type. (See Application at page 1, lines 28-31). Such a system is neither taught nor suggested in the references either singly or combined. The Applicant has designed a polypeptide expression construct and method for producing a heterologous polypeptide that enables the synthesis of a recombinant RNA molecule encoding a 3'UTR, a complementary IRES sequence and a complementary polypeptide. Neither Teycheney nor Basso teach the desirability of a DNA or RNA construct having such a coding sequence. Only upon stimulus or an activating signal, (which can include a second positive strand single-stranded RNA virus encoding an RNA-dependent RNA polymerase) can a transgenic cell comprising the present recombinant RNA transcript of the recombinant DNA then produce a sense strand (complementary RNA copy of the recombinant RNA) encoding an IRES and a heterologous polypeptide. The constructs used in Basso contained a viral leader fused to a reporter gene GUS. The viral leader containing the putative IRES and the GUS were DNA molecules. These DNA constructs were subsequently transcribed *in vitro* and did not provide **a complementary IRES and a complementary polypeptide as presently recited in Claim 236 and 260**. Therefore, there is no teaching or suggestion to provide a DNA molecule which is transcribed by DNA dependent RNA polymerase II to form a recombinant RNA molecule which includes a complementary IRES sequence attached to a complementary heterologous polypeptide sequence that is only converted to a sense coding mRNA upon stimulation and/or activation of a second

positive strand single-stranded RNA virus to avoid leaky expression of a heterologous polypeptide.

Applicant respectfully asserts that neither reference either alone or combined recite all of the elements of Claims 236 and 260 as required under 35 U.S.C. §103(a). Therefore a *prima facie* case of obviousness has not been made. (All claim limitations must be taught or suggested MPEP § 2143.03.)

The Action also alleges that a person of ordinary skill would value the observation that the transgene mRNA that includes a 3'UTR of Lettuce mosaic virus (LMV) could serve as a template for the synthesis of complementary (-) strand RNA following an infection by PepMov as taught by Teycheney. Therefore, the Action alleges it would have been obvious to modify the transgene construct of Teycheney by replacing LMVCP encoding sequence with a sequence complementary to a DNA sequence encoding the gene of interest operably linked to an IRES of Basso resulting in the instant invention. The Applicant respectfully disagrees.

What is particularly telling, is that in the transgenic tobacco line 11C5 which expressed the LMVCP construct comprising the LMV-specific 796 bp fragment, a minus (-) complementary strand of the LMV construct could not be synthesized after infection with TuMV. (Teycheney at page 1124, col. 2, lines 8-14). TuMV was the same plant virus that was studied in Basso, in which it was shown that the TuMV virus had an operable IRES element. Therefore, one of ordinary skill in the art would not have combined the teachings of Teycheney to create a DNA molecule capable of being transcribed into a complementary recombinant RNA molecule expressing a 3'UTR, a complementary IRES and a complementary heterologous polypeptide with the teachings of Basso. The combination of Teycheney and Basso would not have allowed the expression of a heterologous polypeptide. Therefore, one of ordinary skill in the art would not have had any motivation to combine the teachings of Teycheney with the teachings of Basso to arrive at the Applicant's invention.

Accordingly, Applicant respectfully requests that the present rejection of Claims 236-241, 243-257 and 260-274 under 35 U.S.C. §103(a) be reconsidered and withdrawn.

CONCLUSION

Applicant submits that the claimed methods of producing a heterologous polypeptide are not unduly broad – they are focused on DNA constructs that are used to transfect and express the

polypeptides in transgenic plants and cells. Practice of these methods does not require undue experimentation, beyond the level of IRES functionality in specific plant, yeast, insect and animal cells using standard experiments routine in the art. The study of IRES mode of translation in plants yeast and animal cells in particular, were well understood to have utility, and design of such IRES/host cell compatibility analyses were well within the skill of the ordinary artisan at the time of filing. Accordingly, Applicant submits that the claims are fully enabled, and request withdrawal of the rejections under 35 U.S.C. §112.

In addition, it has been shown that the combination of references cited in this Action fail to disclose all of the elements of the independent claims and claims dependent thereon. Furthermore, the combined references lack a credible suggestion or motivation to combine the teachings of the two references to arrive at the claimed invention. Accordingly, Applicant submits that the claims are not rendered obvious over the cited references, and request withdrawal of the rejections under 35 U.S.C. §103(a).

Applicant submits that a full and complete response has been made to the outstanding Office Action and the present application is in condition for allowance. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (248) 641-1600.

Respectfully submitted,

Dated: August 29, 2008

By: _____

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Attachments: Dorokhov and Urwin references